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Note

Intramolecular coupling of conjugated enynes with cyclopropylcarbene–chromium complexes; a complex reaction pathway

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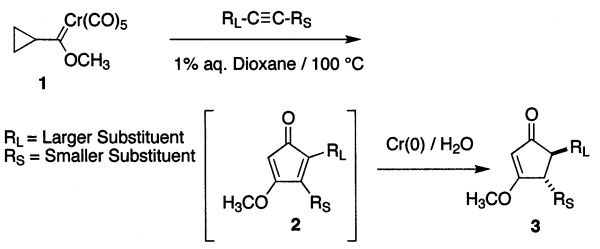
Abstract

The intramolecular coupling of conjugated enynes with cyclopropylcarbene complexes has been investigated. The desired products of the reaction, α-alkenylcyclopentenones, were minor products of the reaction. Competing reaction processes included double bond reduction and allylic C–H activation. Intramolecular coupling of selenium-containing alkynes and cyclopropylcarbene complexes followed by oxidation/elimination provided a more efficient route to α-alkenylcyclopentenones. © 1999 Elsevier Science S.A. All rights reserved.

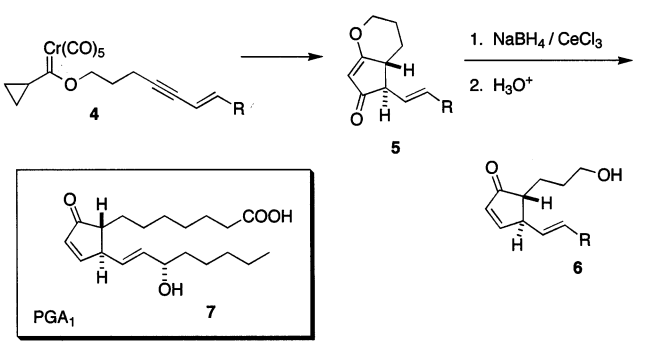
Keywords: Intramolecular coupling; Conjugated enynes; Cyclopropylcarbene complexes; Chromium complexes; Double bond reduction; Allylic C–H activation

1. Introduction

In a series of recent papers, we have demonstrated that 3-alkoxy-2-cyclopentenones (**3**, Scheme 1) are readily prepared from the coupling of alkynes and cyclopropylcarbene–chromium complexes (**1**) [1]. A synthetically very important class of compounds, prostaglandins (exemplified by PGA_1 in Scheme 2), contain structural features very similar to the products



Scheme 1.



Scheme 2.

of these coupling reactions. Our general approach for the synthesis of the prostaglandin ring system [2] is depicted in Scheme 2, which involves intramolecular coupling of the cyclopropylcarbene unit with a conjugated enyne, followed by ring opening[1]. In this paper

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[1] A notable problem with this synthesis is the production of a racemic compound. This problem could be overcome by placement of chiral auxiliaries in the tethering chain; Ref. [1] focuses on these studies.

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our unanticipated observations concerning this coupling are reported.

2. Experimental

2.1. General considerations

NMR (^{1}H and ^{13}C) spectra were recorded on a Bruker AF 200 (200 MHz) or Bruker AF 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). IR spectra were recorded on a Nicolet 5DXC FT-IR spectrometer. Band positions are reported in reciprocal centimeters (cm^{-1}). Band intensities are reported relative to the most intense band and are listed as: br (broad), vs (very strong), s (strong), m (medium), w (weak). Mass spectra (MS) were obtained on a VG 7070E spectrometer using electron impact (EI) or chemical ionization (CI) or on a Hewlett–Packard GC-Mass Spec 5970B with Mass Selection Detector; m/e values are reported, followed by the relative intensity in parentheses. Flash column chromatography was performed using thick-walled glass columns and 'flash grade' silica (Bodmann 230–400 mesh). Routine thin layer chromatography (TLC) was performed by using precoated 0.25 mm silica gel plates purchased from Whatman. Combustion analyses were performed by Galbraith Laboratories (Knoxville, TN) or Desert Analytics (Tucson, AZ). The relative proportion of solvents in mixed chromatography solvents refers to the volume:volume ratio. All commercially available reagents and reactants were obtained in reagent grade and used without purification. All reaction solvents were distilled for purity. Diethyl ether, THF and dioxane were distilled from sodium-benzophenone ketyl and dichloromethane from calcium hydride prior to use. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of nitrogen.

2.2. General procedure I

2.2.1. Synthesis of carbene complexes from alcohols

To the solution of acylate salt **10** [3] (0.40 g, 1.20 mmol) in dichloromethane (20 ml) at 0°C under nitrogen was added acetyl chloride (0.08 ml, 1.20 mmol) via syringe, followed by immediate addition of alkynol (1.20 mmol). The reaction mixture was stirred at 0°C for about 1 h and then warmed to 25°C and stirred for 20 min. The solvent was removed on a rotary evaporator. Flash chromatography of the residue after evaporation using hexane as the eluent gave the pure carbene complex after solvent removal.

2.3. Synthesis of complex *4A*

General procedure I was followed using enyne alcohol **9A** (0.280 g, 1.50 mmol), acylate salt **10** (0.512 g, 1.50 mmol), and acetyl chloride (0.110 ml, 1.50 mmol) in dichloromethane (40 ml). After chromatographic purification, a yellow oil (0.475 g, 74%) identified as carbene complex **4A** was obtained. ^{1}H NMR ($CDCl_3$): δ 7.40–7.20 (m, 5H), 6.90 (d, 1H, $J = 16.2$ Hz), 6.12 (dt, 1H, $J = 16.2$, 2.1 Hz), 5.05 (t, 2H, $J = 6.1$ Hz), 3.50 (m, 1H), 2.60 (td, 2H, $J = 6.8$, 2.1 Hz), 2.20 (tt, 2H, $J = 6.8$, 6.1 Hz), 1.48–1.35 (m, 2H), 1.30–1.16 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 352.1, 223.5, 216.8, 140.9, 136.3, 128.7, 128.4, 126.1, 108.2, 89.7, 81.3, 78.9, 41.5, 28.4, 17.8, 16.5; IR (CH_2Cl_2): 2061, 1979, 1949 cm^{-1}.

2.4. Synthesis of Complex *4B*

General procedure I was followed using enyne alcohol **9B** (0.113 g, 0.90 mmol), acylate salt **10** (0.310 g, 0.90 mmol), and acetyl chloride (0.065 ml, 0.90 mmol) in dichloromethane (20 ml). After chromatographic purification, a yellow oil (0.253 g, 75%) identified as carbene complex **4B** (70:30 *Z:E* mixture) was obtained. ^{1}H NMR ($CDCl_3$): major isomer δ 5.90 (dq, 1H, $J =$ 10.4, 6.2 Hz), 5.02 (t, 2H, $J = 5.6$ Hz), 2.52 (br t, 2H, $J = 6.4$ Hz), 1.83 (dd, 3H, $J = 6.2$, 1.5 Hz); minor isomer δ 6.05 (dq, 1H, $J = 15.2$, 6.4 Hz), 4.99 (t, 2H, $J = 5.6$ Hz), 2.48 (br t, 2H, $J = 5.4$ Hz), 1.73 (dd, 3H, $J = 6.4$, 1.4 Hz); the following peaks are overlapping in both isomers 5.47 (m, 1H), 3.48 (m, 1H), 2.10 (m, 2H), 1.46–1.32 (m, 2H), 1.31–1.13 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 352.0, 223.5, 216.8, 137.8, 110.0, 91.9, 85.5, 78.9, 41.5, 28.6, 17.8, 16.5; IR (CH_2Cl_2): 2061, 1979, 1944 cm^{-1}.

2.5. General procedure II

2.5.1. Intramolecular carbene–alkyne coupling reaction

To a three-neck round-bottom flask equipped with a reflux condenser and rubber septum, under nitrogen, was added toluene (100 ml) and water (1 ml), and the solution was heated to reflux. To this refluxing solution was added a solution of carbene complex in toluene (30 ml) via syringe pump over a period of 4 h. After the addition was complete, the mixture was heated at reflux for an additional 20 h and then cooled to room temperature. The resulting green mixture was filtered through Celite and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 4:1 hexane–ethyl acetate as eluent unless otherwise noted.

2.6. Thermolysis of complex **4A**

General procedure II was followed using 0.475 g (1.10 mmol) of carbene complex **4A** in dioxane. Purification by flash chromatography afforded two compounds. The first fraction (0.133 g, 50%) was identified as saturated side chain derivative **11A** as a *cis–trans* mixture. The second fraction (0.008 g, 3%) was the styryl derivative **5A**.

11A: ^{1}H NMR ($CDCl_3$): δ 7.25–7.04 (m, 5H), 5.25 (s, 1H), 4.38 (m, 1H), 4.12 (m, 1H), 3.02–2.04 (m, 3H), 2.30–2.02 (m, 2H), 2.02–1.80 (m, 3H), 1.80–1.25 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 207.0, 205.7, 190.6, 189.9, 141.7, 141.4, 128.4, 128.3, 125.8, 106.0, 105.9, 68.3, 68.1, 52.6, 47.5, 41.5, 38.5, 34.2, 33.6, 31.7, 30.0, 24.8, 22.7, 20.2; IR ($CDCl_3$): 1681, 1606 cm^{-1}; MS (EI): *m*/*e* 242 (M, 2), 150 (4), 137 (56, 68 (100). HRMS: Calc. for $C_{16}H_{16}O_2$ 242.1307, found 242.1309.

5A: ^{1}H NMR ($CDCl_3$): δ 7.32–7.05 (m, 5H), 6.48 (dd, 1H, J = 15.9, 1.1 Hz), 6.14 (dd, 1H, J = 15.9, 7.6 Hz), 5.30 (d, 1H, J = 1.5 Hz), 4.33 (m, 1H), 4.08 (m, 1H), 2.92 (ddd, 1H, J = 7.6, 4.0, 1.1 Hz), 2.76 (m, 1H), 2.22 (m, 1H), 1.98–1.84 (m, 2H), 1.48 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 203.0, 189.3, 136.8, 133.2, 128.5, 127.5, 126.3, 125.6, 105.9, 68.7, 56.9, 41.9, 24.4, 22.8; IR ($CDCl_3$): 1685, 1604 cm^{-1}; MS (EI): *m*/*e* 240 (M, 39), 211 (4), 69 (100).

2.7. Thermolysis of complex **4B** in dioxane

General procedure II was followed using 0.473 g (1.29 mmol) of carbene complex **4B** in dioxane. Purification by flash chromatography afforded two compounds. The first fraction (0.046 g, 30%) was identified as saturated side chain derivative **11B** as a *cis–trans* mixture. The second fraction (0.007 g, 3%) was assigned as the propenyl derivative **5B**, as a mixture *E* and *Z* and *cis* and *trans* isomers.

11B: ^{1}H NMR ($CDCl_3$): δ 5.28 (d, 1H, J = 0.7 Hz), 4.30 (m, 1H), 4.10 (m, 1H), 2.96–2.59 (m, 2H), 2.57 (m, 1H), 2.21 (q of t, 1H, J = 6.9, 5.9 Hz), 2.08 (m, 1H), 1.87 (m, 1H), 1.53–1.31 (m, 4H), 0.92 (t, 3H, J = 6.9 Hz); Irradiate at δ 2.59:δ 2.08 (dd, 1H, J = 8.8, 3.9 Hz). The spectral data were in agreement with those previously reported for this compound [4].

5B: ^{1}H NMR ($CDCl_3$): δ 5.58 (m, 1H), 5.28 (s, 1H), 5.37 (m, 1H); 4.36 (m, 1H), 4.16 (m, 1H), 2.72 (m, 1H), 2.08–1.86 (m, 4H), 1.70 (d, 3H, J = 6.8 Hz); IR: 1689, 1623 cm^{-1}.

2.8. Thermolysis of complex **4B** in toluene

General procedure II was followed using 0.407 g (1.11 mmol) of carbene complex **4B** in toluene. Purification by flash chromatography afforded three compounds. The first fraction (0.061 g, 45%) was identified as dienal **16**. The compound in the second fraction (0.005 g, 3%) was identified as cyclopentenone **17**. The compound in the third fraction (0.030 g, 20%) was the propenyl derivative **5B**.

16: ^{1}H NMR ($CDCl_3$): δ 9.50 (s, 1H), 6.91–6.60 (m, 2H), 5.72–5.49 (m, 2H), 3.90 (t, 2H, J = 6.6 Hz), 2.10–1.70 (m, 4H), 1.15 (m, 1H), 0.65–0.50 (m, 2H), 0.45–0.30 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 194.6, 151.5, 149.4, 143.0, 133.8, 126.0, 99.9, 65.9, 24.7, 22.6, 11.6, 4.1; IR ($CDCl_3$): 1679 cm^{-1}; MS (EI): *m*/*e* 204 (M, 30), 178 (8), 166 (6), 163 (15); HRMS: Calc. for $C_{13}H_{16}O_2$: 204.1150, found 204.1154.

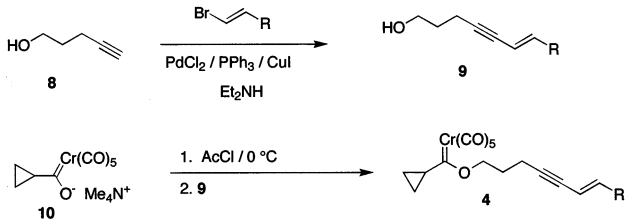
17: ^{1}H NMR ($CDCl_3$): δ 7.44 (t, 1H, J = 2.8 Hz), 3.89 (t, 2H, J = 5.1 Hz), 2.64–2.58 (m, 2H), 2.46–2.40 (m, 2H), 2.15 (t, 2H, J = 6.5 Hz), 1.92–1.75 (m, 2H), 1.41 (m, 1H), 0.76–0.65 (m, 2H), 0.52–0.40 (m, 2H); IR ($CDCl_3$): 1697 cm^{-1}.

2.9. Thermolysis and oxidation/elimination of complex **21A**

General procedure II was followed using 1.030 g (2.00 mmol) of carbene complex **21A** in toluene. Purification by flash chromatography afforded two fractions. The first fraction (0.161 g, 25%) was identified as three of the diastereomers of **22A**. The compound in the second fraction (0.160 g, 25%) was identified as a *cis* diastereomer of cyclopentenone **22A**. The combined mixture of **22A** (0.161 g, 0.500 mmol) was dissolved in methanol (1 ml) and added to a solution of sodium periodate (0.150 g, 0.600 mmol) in 1:1 methanol:water at 0°C. The mixture was stirred at this temperature for 8 h. The mixture was poured into water and ether in a separatory funnel. The ether layer was washed with 1 M sodium hydroxide solution, dried over magnesium sulfate, and the solvent was removed on a rotary evaporator to give 0.050 g (61%) of residue which appeared to be a mixture of isomers of compound **23**. After purification of the residue by flash chromatography, a single isomer (0.033 g, 40%) identified as the *E-trans* isomer was separated.

22A (single isomer fraction): ^{1}H NMR ($CDCl_3$): δ 7.56–7.40 (m, 2H), 7.32–7.10 (m, 3H), 5.05 (d, 1H, J = 1.9 Hz), 4.68 (dd, 1H, J = 8.6, 8.4 Hz), 4.45 (ddd, 1H, J = 11.4, 9.1, 4.7 Hz), 3.45 (dt, 1H, J = 8.0, 6.9 Hz), 3.14 (quintet of d, 1H, J = 6.7, 1.9 Hz), 2.96 (dt, 1H, J = 8.4, 6.9 Hz), 1.41 (d, 3H, J = 6.9 Hz), 2.10–1.30 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 208.7, 194.5, 135.2, 128.9, 127.6, 98.6, 77.9, 47.7, 45.6, 37.3, 25.9, 22.5; IR: 1700, 1696, 1623 cm^{-1}.

23: ^{1}H NMR ($CDCl_3$): δ 5.67 (dq, 1H, J = 15.3, 6.6 Hz), 5.18 (d, 1H, J = 1.2 Hz), 5.13 (ddq, 1H, J = 15.3, 8.5, 1.6 Hz), 4.76 (t, 1H, J = 9.0 Hz), 4.54 (ddd, 1H, J = 11.4, 9.0, 5.1 Hz), 3.30 (m, 2H), 2.15–1.78 (m, 2H), 1.67 (dd, 3H, J = 6.6, 1.6 Hz); IR ($CDCl_3$): 1698, 1620 cm^{-1}. *Anal.* Calc. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.24; H, 7.62%.



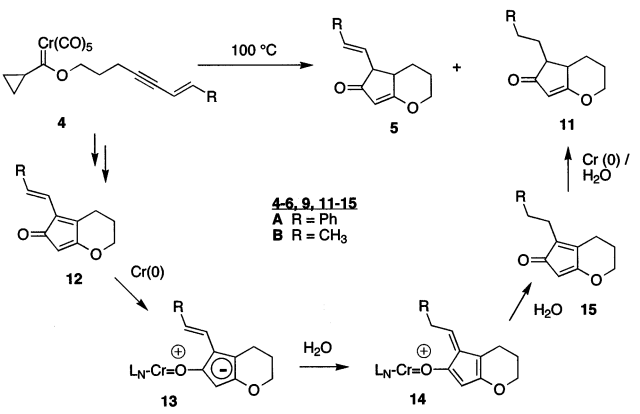
Scheme 3.

3. Results and discussion

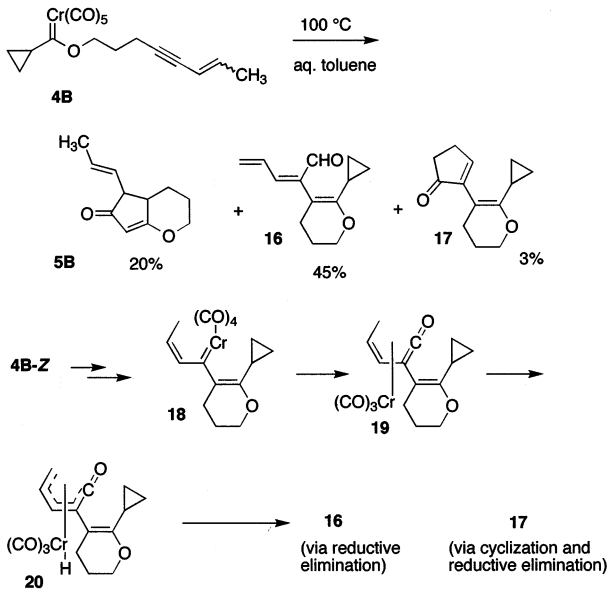
Enyne–cyclopropylcarbene complexes (**4**) were easily prepared using the synthetic route in Scheme 3. Palladium-catalyzed coupling of alkynol **8** and alkenyl halides provided enyne alcohols, which were transformed into the corresponding carbene complexes in good yield using a known procedure [1]. The moderately stable carbene complexes were purified by chromatography and used within a few days.

The intramolecular coupling of enynes and cyclopropylcarbene complexes proved to be a very complex reaction process, resulting in unanticipated reaction pathways (Schemes 4 and 5). Thermolysis of the carbene complex **4A** in dioxane primarily afforded the side chain-saturated compound **11A** (50%) (Scheme 4) accompanied by a trace of the desired product **5A**. A similar result was obtained from thermolysis of the carbene complex **4B** (60:40 *Z:E* mixture), which led to **11B** in 32% yield. Formation of **11** has been attributed to the protonation of the cyclopentadienide intermediate **13** at the side chain, affording intermediate alkoxyfulvene **14**. Hydration/protonation of **14** affords cyclopentadienone **15**, which leads to **11** after a second reduction–protonation sequence [5,6].

Thermolysis of carbene complex **4B** (60:40 *Z:E* mixture) in toluene afforded only a low yield of the desired product **5B** (20%) (Scheme 5). The major product from this coupling was the dienal derivative **16** (45%), accompanied by a trace amount of cyclopentenone **17**



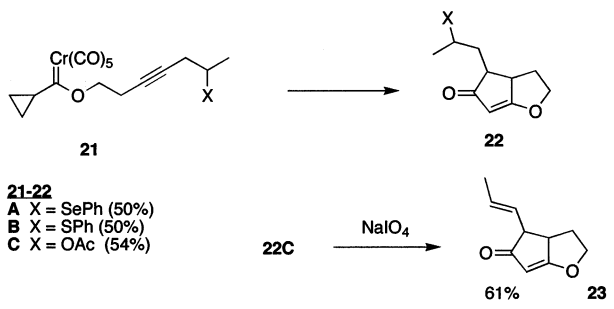
Scheme 4.



Scheme 5.

(3%). The saturated compound **11B** was not observed under these conditions. A mechanism for the formation of **16** and **17** involves activation of the allylic C–H bond in the intermediate vinylketene complex derived from the *Z*-alkene (**19**) [7], followed by reductive elimination of H and pentadienyl to provide aldehyde **16**, or cyclization and reductive elimination to provide cyclopentenone **17** [8]. A previous study revealed that an allylic C–H activation process similar to conversion of **4B**-*Z* to **20** was more favorable in hexane than in THF [8a]. This observation is consistent with our observation that compounds **16** and **17** are more prevalent in toluene, which is less polar and less ligating than dioxane.

Although the direct coupling of enynes and carbene complexes was problematic, 5-alkenyl-2-cyclopenten-1-ones could be prepared by a less direct method. Thermolysis of the functionalized alkyne–carbene complex **21A** provided the anticipated coupling product **22A** without complications (Scheme 6). Oxidation of selenide **22** afforded the alkenyl-substituted cyclopentenone **23** in 61% yield [9]. Similar yields were obtained



Scheme 6.

using the acetate and thiophenyl analogs (**21B** and **C**), however, the elimination step [10] proved to be more problematic in these systems.

In summary, we have shown that synthesis of 5-alkenyl-2-cyclopenten-1-ones via the direct intramolecular coupling of conjugated enynes and cyclopropylcarbene–chromium complexes is not straightforward due to competing processes, including reduction of the double bond and unanticipated reaction pathways of divinylcarbene and/or divinylketene intermediates. The desired compounds can be prepared by an indirect method involving coupling of selenium-containing alkynes, which provide α-alkenylcyclopentenones after oxidation and elimination. A program to better understand and control the reaction pathways from the coupling of substituted enynes and carbene complexes is presently a very important aspect of our current research activities [11].

Acknowledgements

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